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Utilising Heterogeneity: Using a Digital Database of Lung Cancers and Immune Profile to Complement Subjective Assessment

Background

Traditional pathological assessment of tissue sections involves subjective analysis of complex and heterogeneous features, typified by the challenge of 'measuring' PD-L1 expression in non-small cell lung cancer (NSCLC) as a guide to its treatment with immune checkpoint inhibitors. Such heterogeneity is generally perceived as a problem but might, in fact, reflect not only biologically important epitope variation, but also important features of the tumour microenvironment and, by extension, be a tool for predicting behaviour. In-depth analysis of a single slide of a tumour by digital pathology, image analysis and machine learning makes more accurate and meaningful analysis a possibility.

Method

Expression of PD-L1 was assessed by immunochemistry in 250 sections from 137 resected NSCLCs using the Ventana SP263 antibody and a validated protocol and its distribution compared with morphology as revealed by corresponding HandE-stained sections. Slides were scanned to create a digital image using Aperio Scanscope with division of images into 1mm2 squares using QuPath opensource software, each of which was assigned x and y co-ordinates. Squares were assessed subjectively by two pathologists for morphological features and PD-L1 expression and also subject to automatic image analysis including cell counting and membrane detection. Co-ordinates and values were stored in Microsoft Excel and a digital database was generated for every slide. In-depth analysis of digital data points was achieved using "R" software custom algorithms that included simulating biopsy sampling and applying spatial analysis packages.

Result

The resulting database, comprising approximately 30,000 data points from the 137 tumours, is being used to simulate needle-core biopsies, assess heterogeneity of PD-L1 expression and relate this to the tumour micro-environment including immune cell populations, immune signature and tumour mutational burden.

Conclusion

The vast amount of information in every NSCLC cannot be extracted by conventional histopathological analysis. By utilising new technologies and considering alternative paradigms for data acquisition, powerful new approaches may be developed that give information pertaining to not just diagnostic and prognostic features of a tumour, but behavioural traits including likely responses and resistances to novel drugs such as immune checkpoint inhibitors. The methodology described here is an attempt to extract these data in a more objective way and complement the still crucial subjective analysis that is traditionally the prerogative of the histopathologist.